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The first year of treatment predicts the prognosis of asthma over 25 y—A prospective study

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Abstract

Background: An investigator-driven, real-life follow-up study of adult-onset steroid-naïve, newly diagnosed asthma (162 patients) to investigate the treatment results over the 25-year course of the disease and whether the first treatment year's forced expiratory volume in one second (FEV₁) predicts the long-term prognosis.

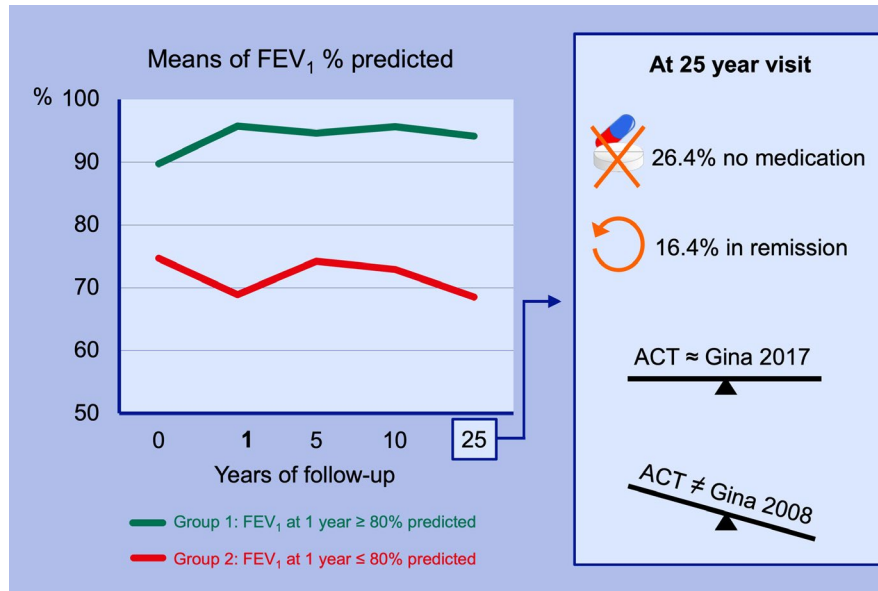
Methods: Eighty-three per cent of the 133 living patients participated in the 25-year examinations. At this visit, basic asthma examinations including lung function, as well as questionnaires for health-related quality of life (HRQoL), GINA and the Asthma Control Test, were used for evaluation. The use of medication and remission was verified.

Results: There was no statistically significant change in mean FEV₁% predicted (FEV₁%) from baseline to the 25-year control. The changes in FEV₁% during the first year predicted the results at the end of follow-up. Normal FEV₁% at the end of the first year predicted normal FEV₁%, and below-normal FEV₁% at 1 year predicted below-normal FEV₁% at 25 years. Twenty-nine patients (26.4%) had discontinued their medication, and six (5.5%) used ICS periodically. Clinical remission was reached by 16.4% of the patients, and 7.6% reached functional remission. The general HRQoL remained unchanged.

Conclusion: In adult-onset asthma, the level of FEV₁ reached during the first treatment year seems to predict the later lung function level. One quarter of the patients discontinued the asthma treatment, but their HRQoL was better than that of those continuing to use ICS. Clinical remission was reached by 16% of the patients, which is in concordance with other studies.

KEYWORDS

adult asthma long-term follow-up, asthma control, asthma remission, health-related quality of life, predicted value of lung function



GRAPHICAL ABSTRACT

In adult-onset asthma, the level of FEV₁% reached during the first treatment year predicts the later lung function level. 26.4% of the patients had discontinued their medication, and 16.4 % were in clinical remission with good HRQoL. The patients' perceptions of their asthma control level were closely aligned as assessed by the Asthma Control Test and GINA 2017, but GINA 2008 yielded discrepancies. Abbreviations: FEV₁: forced expiratory volume in one second; HRQoL: health-related quality of life.

1 | INTRODUCTION

The Global Initiative for Asthma (GINA) has specified the asthma treatment goals: patients should be symptom-free (no more than two symptoms/week) and have good lung function.^{1,2} These goals are challenging: roughly one third of patients have been found to be asymptomatic in long-term follow-up.^{3,4} On the other hand, the results regarding lung function in adult-onset asthma have been inconsistent—there has been either a decline in lung function, no change or even improvement over the years.^{5–10} Although the long-term prognosis seems to be connected to the asthma phenotypes,¹¹ there may be other markers for evaluating the prognosis of asthma.

Asthma is a chronic disease that requires long-term treatment as well as guided self-management to control and modify the treatment; this means that the patients expect asthma management to be useful, including the subjective perception of their asthma control, although these do not always correspond with the level of lung function.^{12,13}

The aim of this investigator-driven, real-life 25-year follow-up study of adult-onset asthma was both to ascertain the long-term treatment results and to investigate whether the forced expiratory volume in one-second percentage of the predicted value (FEV₁%) at the end of the first treatment year predicts the long-term prognosis. Furthermore, the correlation between the patients' assessment of their asthma control and the measured FEV₁% was examined.

2 | MATERIALS AND METHODS

2.1 | Study plan

The study population comprised 162 consecutive newly diagnosed adult-onset asthmatics during 1991–1993 at the South Karelia Central Hospital in Lappeenranta, Finland (Figure 1). The diagnostic criteria for asthma (American Thoracic Society)¹⁴ and the details of the methods have been explained in earlier.¹⁵ The treatment principles used in the beginning of the study differed from today's guidelines (GINA 2017²). All of the asthma patients were on ICS-based treatment from the time of diagnosis (double dose of ICS during the first 2 months). They were educated in peak expiratory flow (PEF)-based guided self-management. All patients were responsible for purchasing their own medication.

The patients attended their local public healthcare centres for routine reviews. The patients still living were invited by letter to participate in a structured review visit. They were informed about the study procedure and asked to sign a written consent to take part in this study.

The Ethics Committee of Helsinki University Hospital approved the current study plan.

2.2 | Study methods

Lung function was measured outside the pollen season by means of flow volume spirometry according to the international standard,

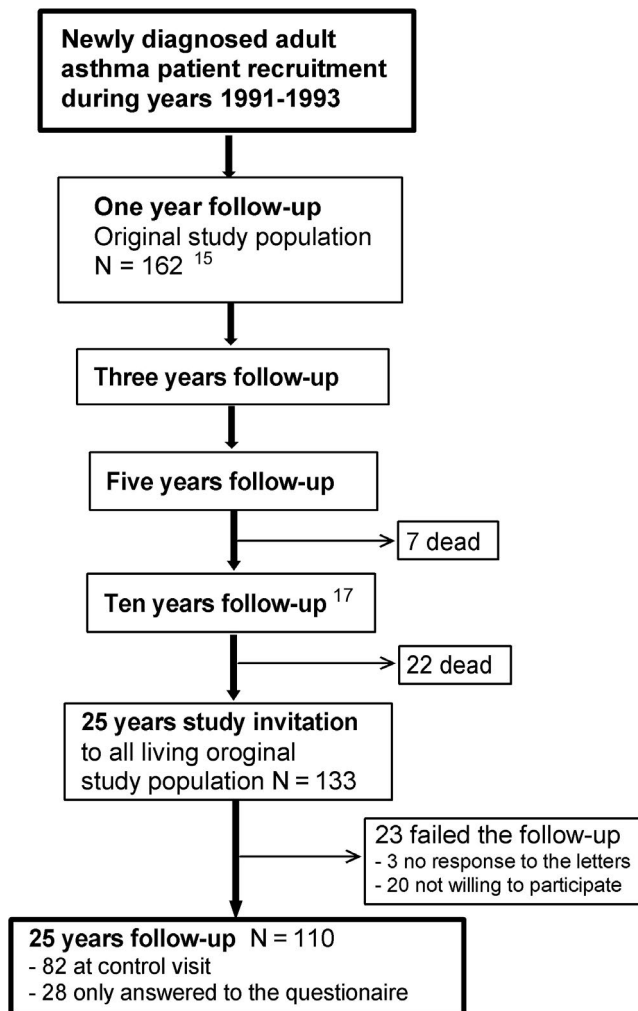


FIGURE 1 Flow chart of the study

using the Medicro Spiromasters Spirostar USB, version 4.3. The results were presented as percentages of the predicted Viljanen values of the normal Finnish spirometry reference range.¹⁶

According to the 10-year results, we noticed that the changes in FEV_1 from baseline (=initial visit) to the first year divided patients into four groups: A = $FEV_1 \geq 80\%$ of the predicted value in both measurements; B = $FEV_1 < 80\%$, at baseline and $\geq 80\%$ at the 1-year control; C = $FEV_1 \geq 80\%$ at baseline but $< 80\%$ at the 1-year control; and D = $FEV_1 < 80\%$ at baseline and at the 1-year control.¹⁷ In the present study, these results are analysed further.

The fraction of exhaled nitric oxide (FeNO) was measured by NioxVero version 2015, updated 2016, with a flow rate of 50 mL/L. FeNO was not performed earlier.

Health-related quality of life (HRQoL) was measured by using both the generic 15D instrument and the disease-specific St George's Respiratory Questionnaire (SGRQ), as explained earlier.^{15,18-20} The mean 15D score of the patients was compared with that of the age-standardized general population.²¹ The 15D data for the general population came from the National Health 2000 Health Examination Survey.²²

Before the 25-year control visit, the patients filled out the Asthma Control Test (ACT) questionnaire²³ and both HRQoL questionnaires. Blood samples for the determination of the eosinophil count and IgE were taken. Skin prick tests were done only at baseline.¹⁵ Later, a letter including the ACT and GINA 2017 questionnaires was sent to those living 28 patients who were unable to attend the review visit.

At the 25-year visit, the patients were examined to check that the baseline diagnostic criteria for asthma were met, and their asthma control was assessed using the criteria of the GINA guidelines from 2008 (used at the 10-year control³) and 2017. The calculation of the medication used was based on patients' reports. Clinical remission was defined as not having used any asthma medication during the last 12 months and being asymptomatic (ACT score and GINA 2017 controlled). The second, functional definition also included normal lung function ($FEV_1 > 80\%$, $FEV_1/FVC > 0.7$, and/or $FeNO < 20$ ppb).

2.3 | Statistical analysis

The outcome variables are reported as means and standard deviations (SD). Differences between groups were tested with independent samples *t* tests or ANOVA (analysis of variance), and when nonparametric tests were needed, Mann-Whitney *U* or Kruskal-Wallis tests were used. Differences between baseline and follow-up results within the groups were tested with paired samples *t* tests or the Wilcoxon signed rank test. Differences between distributions were tested with the chi-squared test. A *P*-value of $< .05$ was considered significant. The analyses were carried out by using the Finnish statistical software PATO, version 4.5 (Mikrovo Oy, Forssa), and the logistic regression analyses by using the GNU PSPP (psppire 0.8.5; <http://www.gnu.org/software/pspp/>).

3 | RESULTS

3.1 | Patient characteristics at baseline and follow-up

Twenty-nine (17.9%) of the 162 patients died during the 25-year period, none of whom due to pulmonary diseases. Out of the 133 living patients, 110 (83%) participated in the present study, including those 28 patients who were unable to attend the review visit.

Out of the patients, 38 (34.5%) were male, and 64 were atopic (58.7%) according to the baseline prick test. At baseline, 16 of the patients enrolled were smokers (< 10 pack years), seven were still smokers at 25 years, and one had started smoking after the 10-year control. At 25 years, the patients had a higher BMI and better FEV_1/FVC than at baseline, but there were no statistically significant differences in FVC or $FEV_1\%$ of predicted (Table 1). The mean blood eosinophil count ($N = 55$ at baseline) decreased statistically significantly from 0.31 (SD 0.18) to 0.21 (SD 0.13). The mean IgE value ($N = 32$) was 120.5 (SD 186.4) at baseline and 259.9 (SD 323.7) at the 25-year follow-up. The changes in eosinophils and IgE were

TABLE 1 Some results of the 25-year follow-up study. Measurements at baseline and at the end of the study period, with the significances of the differences between these values. N = 110 including 29 patients, who only answered the questionnaire

	Baseline Mean (SD)	Follow up Mean (SD)	P-value
Male sex N (%)	38 (34.5)	38 (34.5)	
Atopic persons N (%)	64 (58.7)	ND	
Age, y	36.4 (13.5)	61.4 (13.5)	
BMI, kg/m ²	25.3 (4.0)	28.5 (5.1)	.000
ICS, mg/d	1.13 (0.46)	0.59 (0.59)	.000
FVC, % predicted	96.0 (13.4)	92.5 (18.0)	.194
FEV ₁ , % predicted	86.1 (14.5)	87.1 (20.2)	.764
FEV ₁ /FVC, % predicted	89.3 (9.4)	93.0 (11.5)	.012
Histamine PD ₁₅ , mg	0.21 (0.35)	ND	
FeNO ppb	ND	15.5 (13.1)	
SGRQ total	26.5 (15.7)	13.5 (13.9)	.000
15D score	0.898 (0.096)	0.885 (0.111)	.634
ACT	ND	22.8 (2.9)	

Abbreviations: 15D, Generic health-related quality-of-life instrument; ACT, Asthma Control Test; B-EOS, blood eosinophil count; BMI, Body mass index; FeNO, fraction of NO in exhaled air; histamine PD₁₅, provocation dose of histamine; ICS, inhaled corticosteroid; ND, Not done; SGRQ, St George Respiratory Questionnaire.

statistically significant ($P = .001$). The FeNO was measured only at 25 years, and the mean value was 15.5 ppb (SD 13.1).

The patients lost to follow-up ($N = 23$) differed statistically significantly from those included ($N = 110$) only in baseline mean FVC (% of predicted): 89.7 vs 96 ($P = .040$).

3.2 | Treatment

The daily mean dose of ICS (beclomethasone equal) at baseline was 1.13 mg (SD 0.46). At 25 years, 68% (75 patients) used ICS continuously, with a mean patient-reported dose of 0.81 (SD 0.53), and the change from baseline was statistically significant ($P = .000$). Six patients used ICS periodically, with a mean dose of 0.65 mg (SD 0.76). Twenty-nine patients had stopped using their asthma medication. As an adjunct to ICS, 44 patients (40%) used long-acting sympathomimetics (LABA) and eight a leukotriene antagonist. All patients were advised to take short-acting sympathomimetics (SABA) as needed. Eight persons had used oral corticosteroids for an exacerbation over the last year before the review visit.

The evaluation of the patient-reported ICS doses in relation to asthma control according to GINA 2017 demonstrated that patients whose asthma was controlled used a mean of 0.45 (SD 0.52) mg/d of ICS. This differed statistically significantly ($P = .000$) from those with partially controlled (mean 1.04 mg/d, SD 0.61) or uncontrolled asthma (mean 1.09 mg/d, SD 0.55).

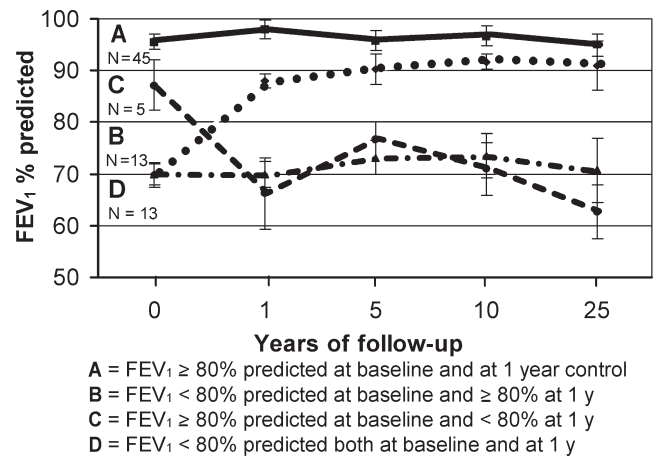


FIGURE 2 Means (± SEM) of FEV₁ values in groups (A–D) according to treatment results during the first year of the 25-year follow-up. Results of patients who participated in spirometry measurements both at baseline and at the end of study

3.3 | Changes in FEV₁% of predicted

In the group as a whole, there was statistically significant change in mean FEV₁% from baseline value 86.1 (SD 14.4) to 90.6 (SD 16.9) at the end of the first year of study (paired t test, $P = .002$) but no statistically significant change in mean FEV₁% from baseline to 25 years (87.1, SD 20.2).

The individual changes in FEV₁% during the first treatment year divided the patients into four groups, labelled herein as groups A–D (Figure 2). They differed statistically significantly in their mean FEV₁% both at baseline and at the 25-year mark: there was an improvement in groups A and B, while the situation worsened in group C (Table 2).

The multivariate binary logistic regression analysis showed that an age of under 30 years at baseline (OR 15.34, 95% CI 1.40–167.66, $P = .025$) and normal FEV₁% after the first year (OR 8.76, 95% CI 1.16–66.04, $P = .035$) were independent predictors of normal FEV₁% at 25 years. The model also included atopy, sex (male), BMI (<23 kg/m²), blood eosinophil count (>250 × 10⁹/L), never smoking, and the baseline histamine provocation test.

All patients in group C were smokers or ex-smokers. This constituted a statistically significant difference ($P = .003$) from the other groups. At baseline, the patients in group D were older (43 years, SD 10.8) than those in the other groups (35–37 years, SD 11.16), but the difference was not statistically significant.

3.4 | Discontinuation of treatment and remission

During the follow-up, 26.47% of the patients (29 patients, 18 of whom before the 10-year visit) had stopped taking all asthma medication. Six patients (5.5%) used medications only periodically (mean dose 0.65 [SD 0.76] mg). The ICS nonusers were younger (mean 57.1 years v. 63.4 years, $P = .022$). Otherwise, there were no statistically significant differences between ICS users and nonusers. Only the nonusers' results improved during follow-up (Table 3).

TABLE 2 Lung functions as % of predicted values at baseline and at 25 y follow-up by groups based on changes in FEV₁ during first year of treatment. Results of patients who participated in spirometry measurements both at baseline and at the end of study

Group	A N = 45 Mean (SD)	B N = 13 Mean (SD)	C N = 5 Mean (SD)	D N = 13 Mean (SD)	ANOVA P-value
FVC baseline	102.3 (10.4)	82.2 (13.9)	92.2 (13.4)	83.1 (7.9)	.000
FVC 25 y	98.0 (13.6)	93.9 (20.4)	75.4 (18.5)	81.1 (21.7)	.002
Change ^a	<0.05	<0.05	NS	NS	
FEV ₁ base line	95.5 (9.8)	69.9 (8.4)	87.2 (10.9)	69.9 (7.4)	.000
FEV ₁ 25 y	94.9 (14.1)	91.1 (17.3)	62.6 (11.6)	70.8 (22.4)	.000
Change ^a	NS	<0.01	<0.05	NS	
FEV ₁ /FVC baseline	91.8 (8.1)	86.5 (10.7)	94.2 (8.6)	84.3 (8.7)	.019
FEV ₁ /FVC 25 y	95.9 (7.5)	97.5 (8.6)	83.6 (8.4)	86.0 (14.1)	.001
Change ^a	<0.01	<0.01	NS	NS	

Note: Groups: A, FEV₁ ≥ 80% of predicted value at baseline and at the 1-year control, B, FEV₁ < 80% of predicted value at baseline and ≥80% at the 1-year control, C, FEV₁ ≥ 80% at baseline and <80% at the 1-year control, D, FEV₁ < 80% at baseline and the 1-year control.

^aSignificance of change from baseline to the 25-year visit, paired samples t test.

The ICS nonusers' mean ACT was 24.1 (SD 1.4), which was statistically significantly better ($P = .002$) than the 22.2 (SD 3.3, $P = .002$)²⁴ of the ICS users. According to the GINA 2008 criteria, the nonusers' asthma was controlled in 72.7% of the cases, and the rest were under partial control ($P = .037$). According to the GINA 2017 criteria, the asthma was controlled in 97% and partially controlled in 3% of the patients ($P = .003$). The improvement in the SGRQ score was statistically significantly better among ICS nonusers (Table 3). Their mean SGRQ score was normal, 5.2. Their mean 15D score was also better at baseline but did not change during the follow-up (Table 3).

The univariate binary logistic regression analysis showed that normal FEV₁% after 1 year of treatment and an age of less than 30 years at baseline were statistically significant predictors of the discontinuation of ICS treatment. Atopy, sex (male), high blood eosinophils (over $0.250 \times 10^9/L$), or normal baseline FEV₁ did not show this effect. In multivariate binary logistic regression analysis with these variables, only normal FEV₁% after 1 year of treatment significantly predicted the discontinuation of treatment (OR 5.53, 95% CI 1.00-28.04, $P = .039$).

At 25 years, 16.4% (18 patients) had reached clinical remission criteria. Functional remission had been achieved by 7.6%.

3.5 | Asthma control and HRQoL

At 25 years, the mean ACT score was 22.9 (SD 3.0). The asthma was controlled in 83.5% of the patients (ACT cut-off score > 20).

According to the GINA 2008 vs 2017 criteria, the asthma was controlled in 57.0% vs 77.3%, partially controlled 25.3% vs 14.5%, and uncontrolled in 17.7% vs 8.2 of the patients, respectively (Table 4).

The total SGRQ score had improved both clinically and statistically significantly from the baseline mean of 26.5 to 13.5, $P < .001$ (Table 1). The mean 15D score of 0.885 was not significantly worse than the baseline value of 0.898 (Table 1). The difference in the mean 15D HRQoL score in comparison with the age-standardized

general population was -0.022, which is clinically important but statistically nonsignificant ($P = .090$). There were little differences between the FEV₁ subgroups A-D; the mean SGRQ score improved statistically significantly in all other subgroups except group C (Table 5).

The univariate or multivariate binary logistic regression analysis showed no predictors of asthma control or remission.

4 | DISCUSSION

4.1 | Study plan and patient characteristics

This study is unique because of the long follow-up time, 25 years (2 750 treatment years), for newly diagnosed adult-onset asthmatics, who were ICS-naïve prior to the diagnosis. At the beginning of the study period, all adult patients with suspected asthma in our area (population 130 000) were referred to the specialist clinic for diagnosis and the starting of treatment. These patients represent the normal, nonselected distribution of asthma patients. Between the study control visits, all of the patients were in a real-life situation and managed by public healthcare centres, which followed the Finnish Asthma programme.²⁵ The same investigator (RK) implemented all study control visits.

Most of the participants were atopic. The mean eosinophil was normal at baseline, but the value changed statistically significantly despite remaining within normal ranges. The clinical meaning of these changes remained unclear. The increase in IgE did not associate with the severity of asthma during follow-up. This finding was not in agreement with those by Tanaka et al²⁶ in their longitudinal study, or those by Jarvis et al²⁷ concerning the change in total IgE with ageing.

It is probable that the missing patients did not cause any bias in our treatment results because the only statistically significant difference between them and the participants was seen in the baseline FVC values.

TABLE 3 Results of BMI, lung function and health-related quality of life at baseline and after 25 years' follow-up by groups based on the use of inhaled corticosteroids

	ICS Continuously N = 75 Mean (SD)	No or periodical ICS N = 29+6 = 35 Mean (SD)	P-value
BMI at baseline, kg/m ²	25.6 (4.2)	24.4 (3.2)	NS
BMI at 25 y, kg/m ²	29.0 (5.2)	27.3 (4.5)	NS
Change ^a	P = .000	P = .000	
FVC baseline, % of predicted	95.3 (13.0)	97.5 (13.9)	NS
FVC at 25 y, % of predicted	90.7 (18.4)	97.3 (16.3)	NS
Change ^a	NS	NS	
FEV ₁ baseline, % of predicted	86.3 (14.6)	85.6 (14.4)	NS
FEV ₁ at 25 y, % of predicted	84.9 (21.1)	92.8 (16.5)	NS
Change ^a	NS	P < .05	
FEV ₁ /FVC baseline, % of predicted	90.1 (9.3)	87.5 (9.7)	NS
FEV ₁ /FVC at 25 y, % of predicted	92.7 (12.7)	94.0 (8.0)	NS
Change ^a	NS	P < .001	
SGRQ baseline	29.0 (16.6)	20.8 (11.6)	.025
SGRQ at 25 y	16.7 (14.9)	5.2 (5.8)	.000
Change ^a	NS	P < .001	
15D score baseline mean	0.885 (0.100)	0.931 (0.076)	.016
15D score at 25 y mean	0.866 (0.117)	0.936 (0.071)	.005
Change ^a	NS	NS	
Histamine PD ₁₅ baseline, mg	0.21 (0.36)	0.21 (0.32)	NS
Histamine at 10 y, mg ^b	0.83 (0.77)	1.00 (0.87)	NS
Change ^a	NS	P < .001	

^aSignificance of the change from baseline to the 25-year visit, paired t test or Wilcoxon.

^bNot done at 25 years.

The proportion of patients who died during follow-up (17.9%) differs from the long-term follow-up studies by Ali et al²⁸ and Lemmetyinen et al,²⁹ spanning 25 and 15 years, respectively. Both demonstrated an increased mortality risk for asthmatics, a possible reason being the development of COPD. In our study cohort, smoking over 10 pack years was an exclusion criterion, and COPD patients with asthma were therefore excluded at baseline.

Half of the smokers included in the study quit smoking during the follow-up, most of them during the first 10 years of follow-up. In the FEV₁ subgroup C, all patients were smokers or ex-smokers, and their FEV₁% decreased to below the normal range during the first treatment year of follow-up. This confirmed the results of previously published studies that the continuation of smoking resulted in a subsequently lower FEV₁% level despite treatment.³⁰⁻³⁶

4.2 | Treatment

From the beginning, the Finnish Asthma Programme²⁵ was followed. The treatment was initiated with a higher dose of ICS then decreased, mostly halved. Later, the patients followed their guided self-management programme, changing the ICS doses as needed. The Finnish Asthma Programme²⁵ differs from the treatment scheme outlined in GINA 2017 (steps upwards).² This is one reason why, in our study, the real severity of asthma cannot be directly calculated according to the patient-reported ICS doses. On the other hand, patients do not always remember ICS doses correctly, as was noticed in our 10-year study, where the patient-reported mean ICS dose was 0.81 mg/d, while the actual purchased amount was 0.44 mg/d.¹⁷ In the present study, the reported mean daily ICS doses were roughly at the same level as those in the study by Vähätalo et al.³⁷ Furthermore, the highest doses were reported by those patients whose asthma was uncontrolled: 1.09 mg/d in our study. The patients with controlled asthma reported using less than half of the daily doses of ICS compared to those with partially or uncontrolled asthma (GINA 2017). This might mean that the patients were able to evaluate their need for ICS. However, the actual adherence should be investigated further. Moreover, we cannot conclude from our results whether the higher ICS doses had any effect on the level of disease control.³⁸ The different types of asthma in terms of biological or inflammatory character and/or endotypes may have an effect on the long-term treatment responses when ICS is used.^{11,39} This aspect could not be investigated in our follow-up study.

4.3 | Changes in FEV₁% of predicted

The main result is that the mean level of lung function (% of predicted) did not decrease during 25 years. This finding is in agreement with previously published treatment studies,³⁻⁵ although opposite results also exist.⁶⁻⁸ In the study by Shimoda et al,⁸ the FEV₁ values improved during the first year of treatment but decreased later on.

In addition, there were two FEV₁ groups (C and D) in which the patients' FEV₁% did not improve. Despite this, some of them subjectively evaluated their asthma as being under control (ACT and SRQoL). According to the GINA 2008 criteria, however, the asthma was at a controlled level in only 56.8% of the patients. Our results and the finding by Melosini et al⁴⁰ demonstrated the limitations of ACT, which yielded different results for the level of asthma control in terms of symptoms. The lung function did not correlate with the ACT scores. This is why information is needed regarding the way

TABLE 4 Results according to GINA 2008 and 2017 criteria at the end of the study by groups based on changes in FEV₁ during the first year of treatment. Results of the patients who participated in spirometry measurements both at baseline and at the end of the study

Group	A N = 45 Mean (SD)	B N = 13 Mean (SD)	C N = 5 Mean (SD)	D N = 13 Mean (SD)	χ^2 P-value
GINA 2008					
Controlled N (%)	34 (75.6)	7 (53.8)	0 (0)	4 (30.8)	.002
Part. con- trolled N (%)	6 (13.3)	3 (23.1)	2 (40.0)	7 (53.9)	
Uncontrolled N (%)	5 (11.1)	3 (23.1)	3 (60.0)	2 (15.4)	
GINA 2017					
Controlled N (%)	38 (84.4)	9 (69.2)	2 (40.0)	11 (84.6)	.333
Part. con- trolled N (%)	4 (8.9)	2 (15.4)	2 (40.0)	1 (7.7)	
Uncontrolled N (%)	3 (6.6)	2 (15.4)	1 (20.0)	1 (7.7)	

in which the FEV₁ level affects the patients' ability to achieve the maintenance control and their perception of their symptoms.^{13,40,41}

One important finding in our study was that the change in FEV₁% during the first treatment year predicted later lung function. We could not find any published studies where a similar long-term result would have been observed, with the exception of our own previous 10-year study (n = 122).¹⁷ This finding should be verified with further studies.

4.4 | Discontinuation of treatment and asthma remission

Among those who stopped using the ICS medication, the level of asthma control was good—their lung function was at least as good and their HRQoL better than among those who continued the treatment. Most of these patients reported having no symptoms,

although the disease was not controlled in all of them according to the GINA 2008 or 2017 criteria. This corresponds with the study by Haughney et al,¹³ but further studies are needed to find out the disease phenotype/endotype of these ICS nonusers with good results. We did not either evaluate the asthma recovery⁴² or determine the duration of symptoms before the diagnosis.⁴³

The question of remission needs further clarification, especially as regards the classification, which has varied in the published studies.^{4,44,45} Our criteria corresponded with those of Tuomisto et al.⁴ The proportion of patients who reached remission was greater in our study than in the study by Tuomisto et al⁴ and nearly the same as in the study by Westerhof et al,⁴⁴ while it was smaller than in the study by Cazzotti⁴⁵ where only the criteria for drug use were the same. In our study, younger age predicted remission, as was also found by Westerhof et al,⁴⁴ but we did not find predictive value for baseline bronchial hyperresponsiveness as they did.

TABLE 5 Health-related quality of life at baseline and after 25 y follow-up by groups based on the changes in FEV₁ during first year of treatment. Results of the patients who answered the questionnaires at baseline and at the end of follow-up and who participated in spirometry measurements at baseline and at the 1-year control

Group	A		B		C		D		Kruskal- Wallis P-value
	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	
SGRQ baseline	24.7 (15.1)	59	33.6 (17.5) ^a	18	25.6 (16.6)	8	25.7 (14.5)	14	.155
SGRQ 25 years	11.7 (13.8)	48	14.9 (17.0)	13	21.1 (15.0)	5	13.9 (11.6)	13	.266
Change ^a	<0.001		<0.01		NS		<0.05		
D15 score baseline	0.911 (0.086)	57	0.875 (0.116)	17	0.890 (0.083)	7	0.877 (0.111)	15	.498
D15 score 25 years	0.889 (0.111)	48	0.868 (0.147) ^a	13	0.888 (0.101)	5	0.901 (0.082)	13	.999
Change ^a	NS		NS		NS		NS		

Note: Groups: A, FEV₁ ≥ 80% of predicted value at baseline and at the 1-year control; B, FEV₁ < 80% of predicted value at baseline and ≥80% at the 1-year control; C, FEV₁ ≥80% at baseline and <80% at the 1-year control; D, FEV₁ <80% at baseline and at 1-year control.

Abbreviations: SGRQ, St George Respiratory Questionnaire; 15D, Generic health-related quality-of-life instrument; NS, not significant.

^aSignificance of change from baseline to the 25-year visit, paired samples *t* test.

4.5 | Asthma control and HRQoL

At the end of the present study, the proportion of patients with controlled asthma according to the GINA 2017 criteria was higher than according to the GINA 2008 criteria (77% vs 57%, respectively). This means that some patients evaluated their asthma as being controlled in spite of a low FEV₁ value. In our 10-year study, 23%–25% of the patients evaluated their asthma as being controlled.³ This raised the need for further studies in order to discover why the control level increased while the mean lung function values remained unchanged. Is it possible that the patients grow accustomed to their disease and to the symptoms or that they have recovered?⁴²

The same observation also applied to the ACT, which gave higher scores than both GINA questionnaires, but the results of the GINA 2017 and the ACT were close to each other. This is in agreement with Bidad N et al¹² and Melosini et al⁴⁰ in that patients might learn to tolerate their symptoms as being part of their asthma and cease to react to them as easily as before. Miedlinger et al⁴⁶ noticed that the GINA and ACT were in accordance with each other in 67% of the cases. However, the ACT was not useful in evaluating uncontrolled asthma.⁴⁷ There is a need in everyday practice for an objective measuring of asthma control, as stated by Miedlinger.⁴⁶ The patients' opinion is important and useful for compliance, but they should understand their treatment objectives.¹³

The mean disease-specific SGRQ score improved, but the mean values were not normal at 25 years. However, patients who discontinued treatment scored a normal mean SGRQ level of 5.3.

The generic 15D instrument confirmed that the HRQoL was worse among asthmatics than among the age-standardized general population. As far as we know, there are no previously published studies where the HRQoL of patients was followed for 25 years.

In conclusion, in adult-onset asthma with ICS used from the time of diagnosis, the mean FEV₁ expressed as a percentage of the predicted value did not decrease over a 25-year period. The level of lung function reached during the first year of treatment seemed to predict the later lung function level, which would emphasize the importance of the first year of treatment. The asthma was under good control according to the GINA criteria and the ACT, although the HRQoL was mildly decreased. Nearly one third of the patients discontinued their asthma treatment. According to the clinical criteria, the remission rate was 13%, and when lung function was included, the rate was 7.6%. Those in remission had a better HRQoL than those continuing the use of ICS.

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CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest which concerns this study.

AUTHORS' CONTRIBUTIONS

All authors were involved in the study conception and design. RK carried out the clinical examinations of the patients and recorded all results. VV conducted all statistical analyses. HS is the developer of the 15D instrument. RK and VV wrote the manuscript, and all authors were involved in revising it and accepted the final version.

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